

09/269999

510 Rec'd PCT/PTO 05 APR 1999

Attny Docket No. S1011/20102

**TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371**

(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

International Application No. : PCT/GB97/02705
International Filing Date : 01 October 1997
Priority Date Claimed : GB 9620752.7
Filed 04 October 1996
Title of Invention : PRODUCTION OF POROUS ARTICLES
Applicant(s) for DO/EO/US : Robert Terence SMITH and
Rodney Martin SAMBROOK

Box PCT
Commissioner of Patents and Trademarks
Washington, D.C. 20231

Attention: EO/US

Sir:

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. This express request to immediately begin national examination procedures (35 U.S.C. 371(f)).
3. A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

4. A copy of the International Application as filed (35 U.S.C 371(c)(2)) has been transmitted by the International Bureau. A copy of the international application as published under International Publication No. WO 98/15505 is enclosed.
5. Written Opinion dated August 6, 1998, and Response thereto, dated December 15, 1998.
6. Notification Concerning Informal Communication with the Applicant dated December 12, 1998
7. Preliminary Examination Report dated February 15, 1999.
8. A FIRST preliminary amendment.
9. Abstract.
10. Information Disclosure Statement, PTO Form 1449 and copies of references cited therein.

The Declaration and Assignment will follow at a later date.

11. The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492(1)(1)-(5):

Claims Fee	For	Number Filed	Number Extra	Rate	Calculation
	Total Claims	10	0	x 18	\$
	Independent Claims	1	0	x 78	
	Multiple Dependent Claims			x260	
Basic Fee	U.S. PTO was not International Preliminary Examination Authority. Search report on the international application was prepared by the European Patent Office				\$ 970
	Total of above Calculations				\$ 970
	Reduction by ½ for filing by small entity				\$
	Subtotal				\$
	TOTAL NATIONAL FEE				\$ 970

Please charge counsel's account no. 03-0075 in the amount of \$970, or any additional amount which may be required, to cover the above fees. A duplicate copy of the calculation sheet is enclosed.

AUTHORIZATION TO CHARGE ADDITIONAL FEES

The Commissioner is hereby authorized to charge the following additional fees which may be required by this paper and during the entire pendency of this application to counsel's deposit account no. 03-0075:

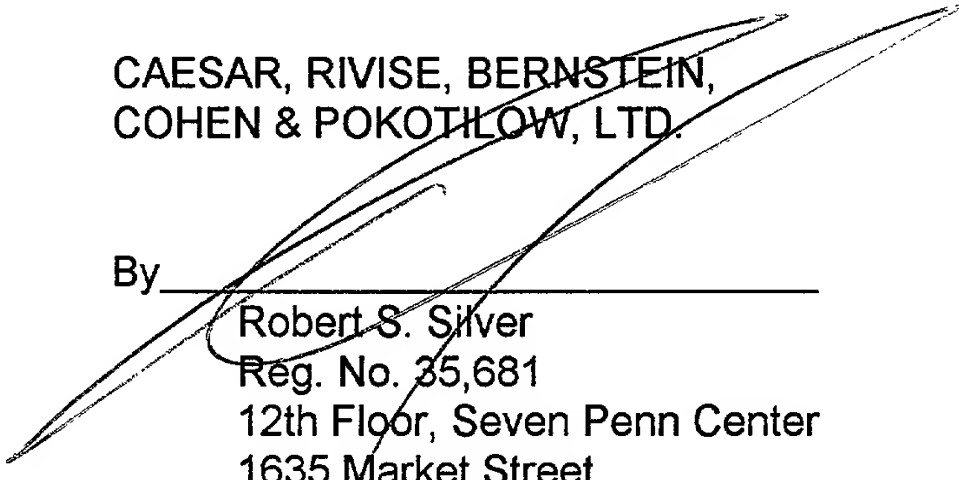
1. 37 CFR 1.492(a)(1), (2), (3) and (4) (filing fees)
2. 37 CFR 1.492(b), (c) and (d) (presentation of extra claims)
3. 37 CFR 1.17 (application processing fees)
4. 37 CFR 1.492(e) and (f) (surcharge fee for filing declaration and/or filing an English translation of an International Application later than 30 months after the priority date)

This application and items attached are being transmitted before the 30 month claimed priority date.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

By


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PATENT
Attny Docket No. S1011/20102

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION

Applicants : Robert Terence SMITH and
Rodney Martin SAMBROOK

Filed : April 5, 1999

Invention : PRODUCTION OF POROUS ARTICLES
U.S. national stage application
based on PCT/GB97/02705,
filed October 1, 1997

PRELIMINARY AMENDMENT

Box PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

Attention: DO/EO/US

Sir:

IN THE CLAIMS:

Cancel Claims 1-10, without prejudice, and add Claims 11-20, attached hereto.

REMARKS

Claims 11 through 20 remain in this application.

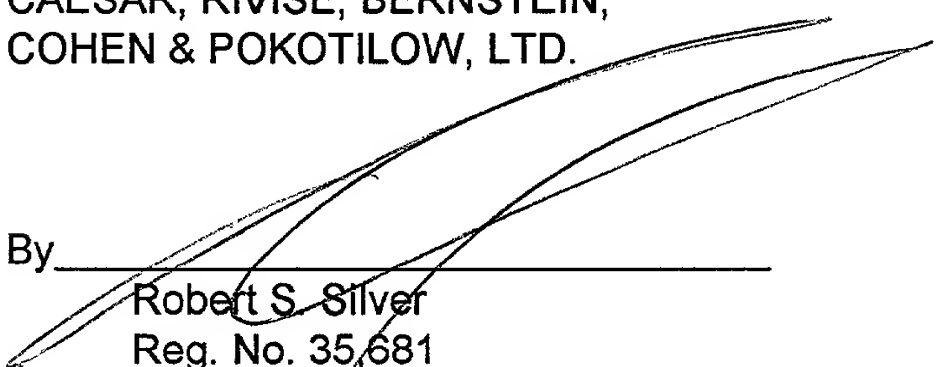
Claim 1-10 have been replaced by Claims 11-20 to eliminate multiple dependency
included in the originally filed claims, and to conform with U.S. practice.

The Abstract of the Disclosure is attached hereto to comply with the requirements
of 37 C.F.R. §1.72(b).

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

April 5, 1999

By 
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Attorneys for Applicant

CLAIMS

11. A method of making a porous article comprised of bonded particles, the method comprising the steps of:
 - 1) forming a dispersion comprising a liquid carrier and the particles and a polymerisable monomeric material;
 - 2) adding a surfactant in a concentration according to the desired density of the porous article and then introducing bubbles of gas with agitation to form a foam and allowing or causing the bubbles to coalesce to form cells some of which form struts;
 - 3) polymerising the monomeric material;
 - 4) drying the structure to remove the liquid carrier and provide a solid article having pores derived from the bubbles; and
 - 5) firing the article to provide a ceramic bond and to remove organic material present, whereby the porous article formed has a porosity of 20% to 95% and comprises cell walls and struts defining pores of pore sizes in the range of 15 to 150 micrometres.
12. A method according to Claim 11, wherein the cells of the foam are adjusted to provide pore sizes greater than 150 micrometres.

13. A method according to Claim 11 including the step of controlling the onset of polymerisation by adjustment of the addition levels of the initiator and catalyst for polymerisation of the monomer to influence the growth of the foam structure.
14. A method according to Claim 13, wherein the onset of polymerisation is controlled by adjustment of the concentration of oxygen to influence the growth of the foam structure.
15. A method according to Claim 14, wherein the period until onset of polymerisation is between an instantaneous polymerisation and 20 minutes.
16. A method according to Claim 11, including the step of applying a partial vacuum to a foam before the commencement of polymerisation until after the end of polymerisation, after which the foam is brought back to atmospheric pressure to increase the size of cells in the foam.
17. A method according to Claim 11, wherein the firing is carried out at 1250°C or 1350°C for two hours.
18. A method according to Claim 11, wherein the particles are hydroxyapatite.
19. A method according to Claim 11, including the subsequent step of growing bone cells in the porous ceramic product.
20. A method according to Claim 11, including adding a drug to the pores of the article.

Sociodemographic characteristics	
Age (mean \pm SD)	36.2 \pm 10.1
Gender	
Male	100
Female	100
Marital status	
Married	100
Single	100
Education level	
High school or below	100
College or above	100
Occupation	
Managerial	100
Professional	100
Technical	100
Service	100
Unemployed	100
Retired	100
Income (US\$)	
< 1000	100
1000-2000	100
> 2000	100
Health insurance	
Private	100
Public	100
None	100
Smoking status	
Smoker	100
Non-smoker	100
Alcohol consumption	
Drinker	100
Non-drinker	100
Exercise	
Regular	100
Irregular	100
None	100
Family size	
< 3	100
3-5	100
> 5	100
Family structure	
Single-parent	100
Two-parent	100
Family income	
< 1000	100
1000-2000	100
> 2000	100
Family health insurance	
Private	100
Public	100
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Family smoking status	
Smoker	100
Non-smoker	100
Family alcohol consumption	
Drinker	100
Non-drinker	100
Family exercise	
Regular	100
Irregular	100
None	100
Family size	
< 3	100
3-5	100
> 5	100
Family structure	
Single-parent	100
Two-parent	100
Family income	
< 1000	100
1000-2000	100
> 2000	100
Family health insurance	
Private	100
Public	100
None	100
Family smoking status	
Smoker	100
Non-smoker	100
Family alcohol consumption	
Drinker	100
Non-drinker	100
Family exercise	
Regular	100
Irregular	100
None	100

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PRODUCTION OF POROUS ARTICLES

The invention relates to the production of articles of controlled porosity.

In our European patent B-0598783 (Agent's ref: P00914EP) there is described and claimed a method of making a porous refractory article composed of refractory particles, the method comprising the steps of:

- a) forming a dispersion comprising particles in a liquid carrier and containing a polymerisable monomeric material
- b) introducing gas into the dispersion.
- c) polymerising the foamed structure,
- d) drying, to remove the liquid carrier to provide a solid article having pores derived from the bubbles; and
- e) firing to remove the organic binder and to provide a ceramic bond.

Preferably the monomeric material is selected to polymerise by cross linking, whereby the liquid carrier and ceramic particles are held within the polymerised structure. In that disclosure there is mention that surfactants may be added to the dispersion to prevent premature settling of solids in the dispersion or to control the foaming characteristics. In Example IX Teepol surfactant is added to the dispersion. The foam was allowed to polymerise and ultimately sintered at 1450°C for two hours.

The method of this prior patent is arranged to produce a variety of useful articles such as catalyst supports, flame supports; gas filters; air fresheners; ceramic armour; diesel particulate traps; insulation materials; artificial parts for the body; metal filters, reusable filters; liquid filters; storage and transportation for flammable and/or toxic materials, humidity sensors, chromatography; filter candles for filtration of hot combustion gases, diaphragms, membranes, refractory separators, phase dividers and electrolytes for high temperature fuel cells.

In our patent publication WO95/30631 (PCT/GB95/01063, Agents Ref. P01204PCT) there is described and claimed a method of making a porous refractory article, the method comprising the steps of:

- forming an aqueous dispersion of refractory particles including a polymerisable monomer component which on polymerisation generates an exotherm
- adding a thermally activated gas generating substance
- adding agents such as initiator and/or catalyst to cause the polymerisation
- adjusting the temperature and/or pressure so that the gas generating substance generates the gas before or during the initial stage of polymerisation of the monomer component whereby the gas forms bubbles which under the heat of the exotherm interconnect to form an interconnected open pore structure.

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By controlling the temperature and pressure the decomposition rate of the gas generating substance is controlled. This in turn provides a means of controlling the density of the end product. In this disclosure TRITON X-100, a surfactant was added as the last ingredient to the dispersion to stabilise the foam.

It is one object of the invention to provide a method of making a porous article having controlled levels of porosity, interconnectivity, pore size, and mechanical properties suitable for use in various applications.

In one aspect the invention provides a method of making a porous article comprised of bonded particles, the method comprising the steps of:

- 1) forming a dispersion comprising a liquid carrier and the particles and a polymerisable monomeric material;
- 2) adding a surfactant in a concentration according to the desired density of the porous article and then introducing bubbles of gas with agitation to form a foam and allowing or causing the bubbles to coalesce to form cells some of which form struts;
- 3) polymerising the monomeric material;

- 4) drying the structure to remove the liquid carrier and provide a solid article having pores derived from the bubbles; and
- 5) firing the article to provide a ceramic bond and to remove organic material present, whereby the porous article formed has a porosity of 20% to 95% and comprises cell walls and struts defining pores of pore sizes in the range of 15 to 150 micrometres.

The dispersion comprises particles having an average particle size less than about 5 micrometres and preferably 95% of the particles will be less than about 2 micrometres.

Advantageously surfactants (which can be cationic, anionic or non-ionic) are present in the dispersion. In low viscosity systems where the ability of a system to foam is controlled by the surface tension, the surfactant type and concentration can have a direct influence not only on the level of porosity within the system but also the pore size and the interconnectivity. The concentration of surfactant can be used to influence the bubble size within a foam and the rate of coalescence, both of which can be used to influence the final pore size.

By controlling the rheology of the suspension it is possible to influence the rate of coalescence of the foam structure. A slurry which exhibits a low degree of pseudoplasticity coupled with a low bulk viscosity is susceptible to foam collapse and rapid bubble growth. In contrast a slurry which exhibits a high degree of pseudoplasticity is subject to long term stability and a less rapid bubble growth although at an acceptable level. As the bulk viscosity of the system increases the controlling effect of the surfactant diminishes.

Another factor which influences the growth of the foam structure is the period before the onset of polymerisation. This period can be controlled by the addition levels of the initiator and catalyst. By controlling these levels as well as the oxygen concentration within the foaming gas the length of time before polymerisation starts can be controlled between an instantaneous polymerisation and one which starts after a period, which can be up to 20 minutes or more. Our evaluations suggest that this period has a major influence on cell structure where the porous article is to be used as a bone substitute.

In a further feature of the invention the process of increasing the cell size within a foam can be encouraged by the application of a partial vacuum to a foam before the commencement of polymerisation until after the end of polymerisation. At the end of polymerisation the stable foam is brought back to atmospheric pressure. This additional step to the foaming process can be used to increase the rate at which the final desired large cell size can be achieved.

Other additives may be present, e.g. viscosity control agents, reinforcing fibres or particles, retarders for polymerisation; and the like.

The bubbles of gas may be introduced in any convenient way, although the preferred methods are listed in our previous patent. The gas used for foaming can be air, although an inert foaming gas such as nitrogen or argon is preferred. To produce a foam with a large pore structure and a high degree of porosity, one could either introduce bubbles of the correct size and quantity into the suspension or cause smaller bubbles to grow by a process of coalescence. The latter is preferred at the moment.

In order to produce the small bubbles within the foam mechanical agitation is preferred.

Our investigations have shown that the structure of the foam can be broken into four distinctly different areas:

- the cells or bubbles

- the struts
- the windows, and finally
- the particulate microstructure

These structures can be seen in Figure 1 of the accompanying drawings and are explained as follows.

A number of cells can be seen in the left hand photo in Figure 1. These cells are formed as a result of introducing a gaseous phase into the ceramic suspension. Where these cells touch there is a tendency for the cell to change shape to maximise the packing density and for the slurry to drain from the point of contact towards the strut. A strut can be seen in the top right hand photo in Figure 1. These struts are the building block for the foam structure. At the point of contact between each cell a thin film of liquid exists. During the later gelling and binder burnout steps this film is removed to leave what we call the cell "windows". These are the connecting holes which interlink adjacent cells and can be clearly seen in the left hand photo in Figure 1. The final structure is that which forms the cell walls and struts.

It is a feature of the invention that the final articles formed consist essentially of the starting ceramic materials only, so avoiding the need for the removal of residual secondary e.g. inorganic binders. The article can thus consist of ingredients acceptable for medical use, e.g. as bone grafts for orthopaedic, surgical, dental and like uses both for humans and animals. There will always be a need to replace bone lost as a consequence of traumatic or non-traumatic events. Bone substitute materials are

available and approved for clinical use. These materials have been successfully used in orthopaedics, dentistry and facial plastic surgery. Among the types of bone graft materials used, particular interest has been shown in the porous types which can provide a scaffold for in growth of connective tissue and bone. Studies have shown that pore sizes less than 10 micrometre prevent ingrowth of cells, pore sizes of 15 to 50 micrometre encourages fibrovascular ingrowth; pore sizes of 50-150 micrometre result in osteoid formation; and pore sizes greater than 150 micrometre facilitate the ingrowth of mineralized bone. Different approaches have been taken to try and mimic the hydroxyapatite frame work within both the cortical and cancellous bone. One material is based on the conversion of a coralline structure to hydroxyapatite material. With this process the selection of the coral with the correct pore structure is imperative before conversion takes place. Two corals were eventually selected exhibiting two different pore structures. These two pore structures are intended to replicate the different structures in cortical and cancellous bone. It is a feature of this invention that synthetic articles made by the method may be used as bone graft materials of high acceptability.

Hydroxyapatite $[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]$ is an ideal candidate starting material. This material belongs to a group of calcium phosphates which are being considered as bone substitute materials. The invention is applicable to hydroxyapatite and any other calcium phosphate (where the Ca/P atomic ratio may vary widely). In addition to this group of materials it may be advantageous to create an interconnected structure in another ceramic material such as alumina or zirconia for mechanical property reasons and either use the material as produced, or coated with a more bioactive material such

as hydroxyapatite. It is another feature of this invention that the materials known as "Bioglass" could be converted in highly porous structures using this method.

The polymerisation preferably proceeds by crosslinking of reactive organic monomers. Examples include acrylates, such as ammonium acrylate or hydroxyethyl methacrylate; or the like. Preferably the monomers are dissolved in water or other liquid carrier to give a premix solution. To this solution are added an initiator and either heat or a catalyst are used to induce free radical vinyl polymerisation. In another variation, the dispersion includes a monosaccharide such as galactose, which can be condensed to form a dimer, trimer or polymer, to have the same effect.

The foamed composition may be allowed or caused to acquire sufficient green strength to allow it to be moved from the parent container or mould. The composition may be subjected to drying to drive off the liquid. In the case of water, drying can be carried out below about 100°C in an oven or using high frequency drying equipment.

The pore sizes in the formed article can be controlled remarkable uniform to yield a material with a pre-determined pore size and level of interconnectivity. The true porosity may range from about 20% to about 95%. The article formed is relatively robust after polymerisation and strong enough to be machined after removal of the liquid carrier.

The firing temperature and duration are selected according to the nature of the particles, e.g. alumina generally requires a higher sintering temperature than hydroxyapatite.

In one more specific aspect the invention provides a method of making a porous article composed of bonded particles, the method comprising the steps of:

- a) forming a dispersion comprising a liquid carrier and the particles and a polymerisable monomeric material;
- b) forming a foam of the dispersion;
- c) polymerising the foamed structure
- d) drying the structure to remove the liquid carrier and provide a solid article having pores derived from the bubbles, and
- e) firing the article to remove the organic binder and provide a ceramic bond.

characterised in that small bubbles of gas are introduced in the dispersion with agitation to form the foam and are allowed or caused to coalesce before the polymerisation, and in that the firing is carried out at a temperature appropriate to the growth of bone cells.

It is a feature of this invention to provide an article having a highly microporous structure if the sintering procedure is controlled. This microporous structure can have advantages in certain applications e.g. it may be infilled with certain drugs such as

antibiotics or growth factors, to act as a slow release agent at the site of an implant and it appears to encourage the easy attachment of in-growing bone cells compared to a dense microstructure.

The formed article may be in a variety of shapes, e.g. in the form of granules, bars, cylinders or rods, blocks or the like.

In order that the invention may be well understood it will now be described by way of illustration only by reference to the following examples and micrographs:

Example I

Hydroxyapatite powder, ammonium acrylate monomer, methylenebisacrylamide, water, the ammonium salt of polyacrylate and the ammonium salt of polymethacrylate were mixed together to form a slurry which was subjected to a high shear mixer in order to remove any agglomerates within the slurry. This was transferred to a glove box within which the oxygen concentration was approx. 0.1%. A surfactant TERGITOL TMN10 was introduced into the slurry and the whole was agitated in a mixer designed to introduce air so that a foam will be formed. The amount by which the ceramic solid is foamed is dependant on the final density required, the solids content of the slurry and the shrinkage which will occur at the later stages of drying and firing. The amount of surfactant added determines the extent of foaming, and this was selected to achieve the required final density. Once the foam density was achieved, ammonium persulphate (initiator) and tetramethylethylenediamine (catalyst)

were injected into the foam to cause the acrylate monomer to start to polymerise. The time before the onset of polymerisation was about 1.5 minutes.

The mixture was restirred and allowed to stand. Polymerisation began after about 1.5 minutes. A photo of the microstructure produced after an idle time of 1.5 minutes is shown in Figure 2. Once polymerised the foam was removed from the mould and allowed to dry at room temperature for 2 days before being forced dried at 60° C in an oven.

At this point the "green" ceramic can easily be machined into the desired shape. The "green" article was heated in a furnace to remove the organic binder and to cause the ceramic microstructure to densify. The sample was split in two and fired at two different temperatures. Sample 1 shown in Figure 3 and sample 2 in Figure 4 were fired at 1250° C for 2 hrs and 1350° C for 2 hrs respectively. It can be seen that the degree of microstructural densification can be adjusted with the sintering conditions. Sample 1 exhibits a highly connected microstructure whereas the microstructural porosity has been removed in sample 2. Live human bone cells were cultured. Both samples 1 and 2 were immersed in the cultures and Figures 5 and 6 show the results after 36 hrs immersion for sample 1 and 2 respectively. The bone cells can be clearly seen on the surface of the cell walls. From these Figures it appears easier for the bone to grow within the undersintered microstructure than the fully densified structure.

Example II

The method of Example I was repeated except that the rate of addition of the initiator and the catalyst were selected so that the time before onset of polymerisation was 16 minutes instead of 1.5 minutes. A highly porous foam exhibiting a larger cell size as shown in Figure 7 resulted. It can be seen from the different Figures that the time before the onset of polymerisation has had a major influence on the cell structure.

The Figures of the accompanying drawings are microphotographs as follows:

Figure 1 is a general foam;

Figure 2 is a foam produced in Example I taken after an idle time of 1.5 minutes;

Figure 3 is the polymerised foam of Example I fired at 1250°C for 2 hours;

Figure 4 is the polymerised foam of Example I fired at 1350°C for 2 hours;

Figure 5 is the fired product shown in Figure 3 after being immersed in a bone cell culture for 36 hours;

Figure 6 is the fired product shown in Figure 4 after being immersed in a bone cell culture for 36 hours; and

Figure 7 is the foam produced in Example II.

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CLAIMS

1. A method of making a porous article comprised of bonded particles, the method comprising the steps of:
 - 1) forming a dispersion comprising a liquid carrier and the particles and a polymerisable monomeric material;
 - 2) adding a surfactant in a concentration according to the desired density of the porous article and then introducing bubbles of gas with agitation to form a foam and allowing or causing the bubbles to coalesce to form cells some of which form struts;
 - 3) polymerising the monomeric material;
 - 4) drying the structure to remove the liquid carrier and provide a solid article having pores derived from the bubbles; and
 - 5) firing the article to provide a ceramic bond and to remove organic material present, whereby the porous article formed has a porosity of 20% to 95% and comprises cell walls and struts defining pores of pore sizes in the range of 15 to 150 micrometres.
2. A method according to Claim 1, wherein the cells of the foam are adjusted to provide pore sizes greater than 150 micrometres.

3. A method according to Claim 1 or 2, including the step of controlling the onset of polymerisation by adjustment of the addition levels of the initiator and catalyst for polymerisation of the monomer to influence the growth of the foam structure.
4. A method according to Claims 1, 2 or 3, wherein the onset of polymerisation is controlled by adjustment of the concentration of oxygen to influence the growth of the foam structure.
5. A method according to Claim 4, wherein the period until onset of polymerisation is between an instantaneous polymerisation and 20 minutes.
6. A method according to any preceding Claim, including the step of applying a partial vacuum to a foam before the commencement of polymerisation until after the end of polymerisation, after which the foam is brought back to atmospheric pressure to increase the size of cells in the foam.
7. A method according to any preceding Claim, wherein the firing is carried out at 1250°C or 1350°C for two hours.
8. A method according to any preceding Claim, wherein the particles are hydroxyapatite.
9. A method according to any preceding Claim, including the subsequent step of growing bone cells in the porous ceramic product.

10. A method according to any of Claims 1 to 8, including adding a drug to the pores of the article.

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P1885.CLAIMS

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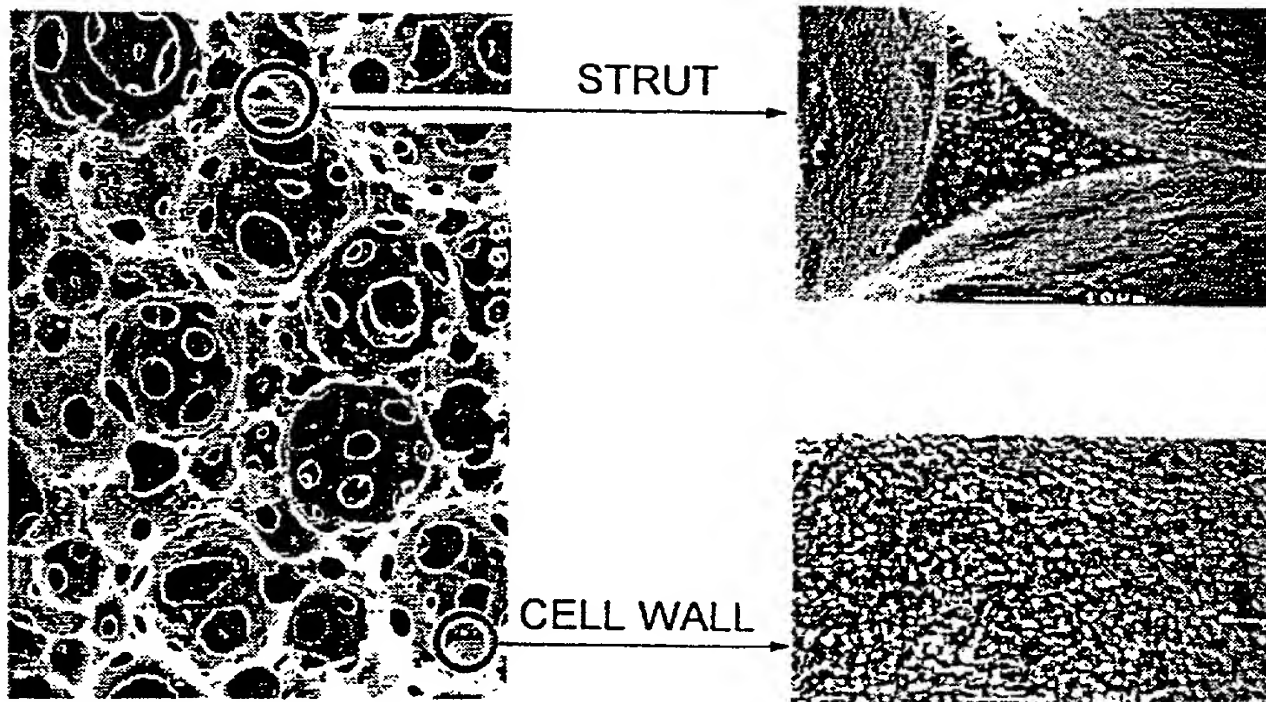


FIG. 1

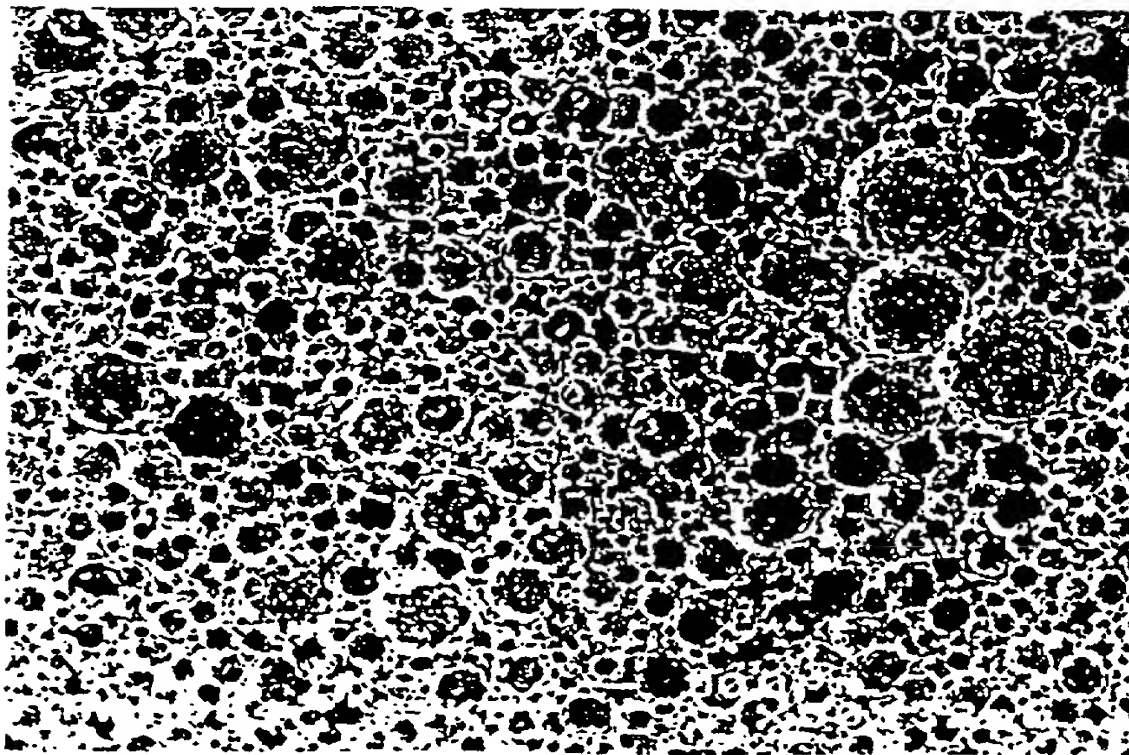


FIG. 2

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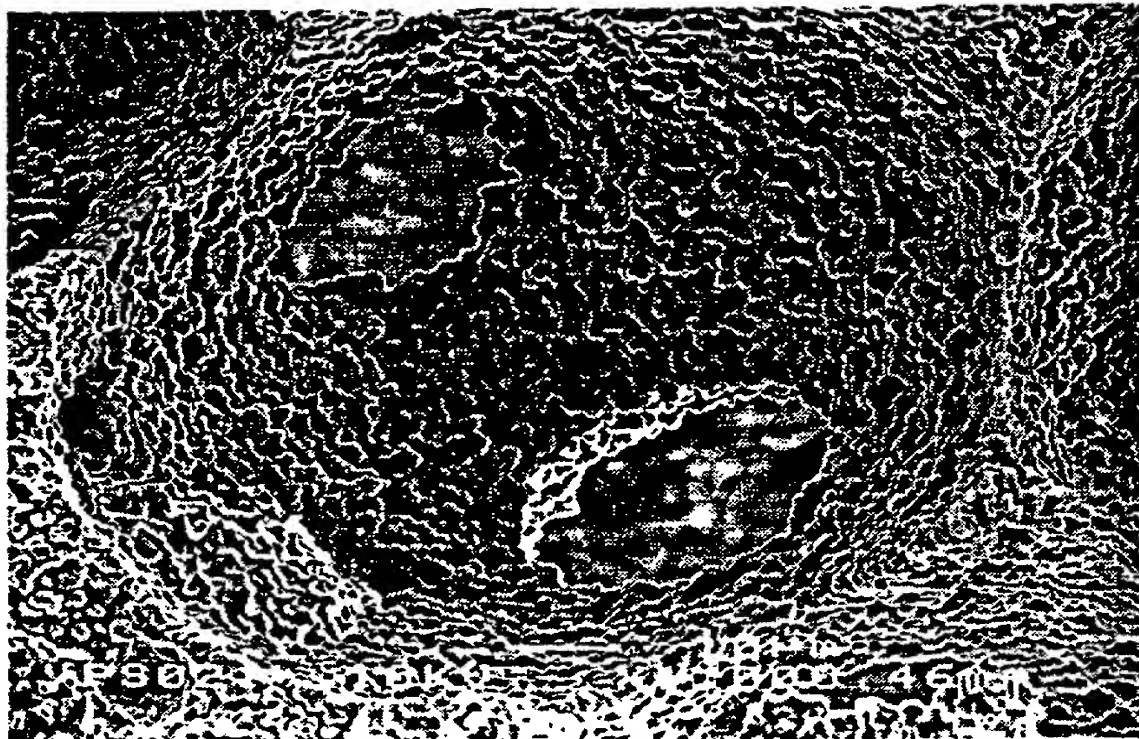


FIG. 3

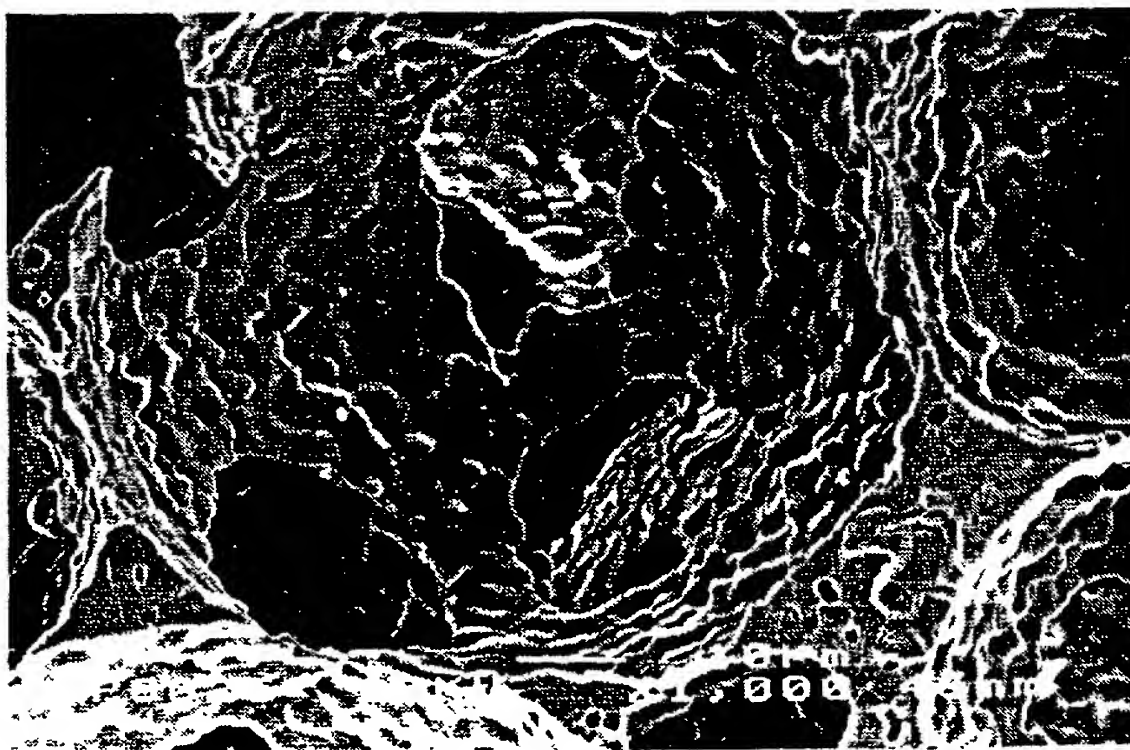


FIG. 4

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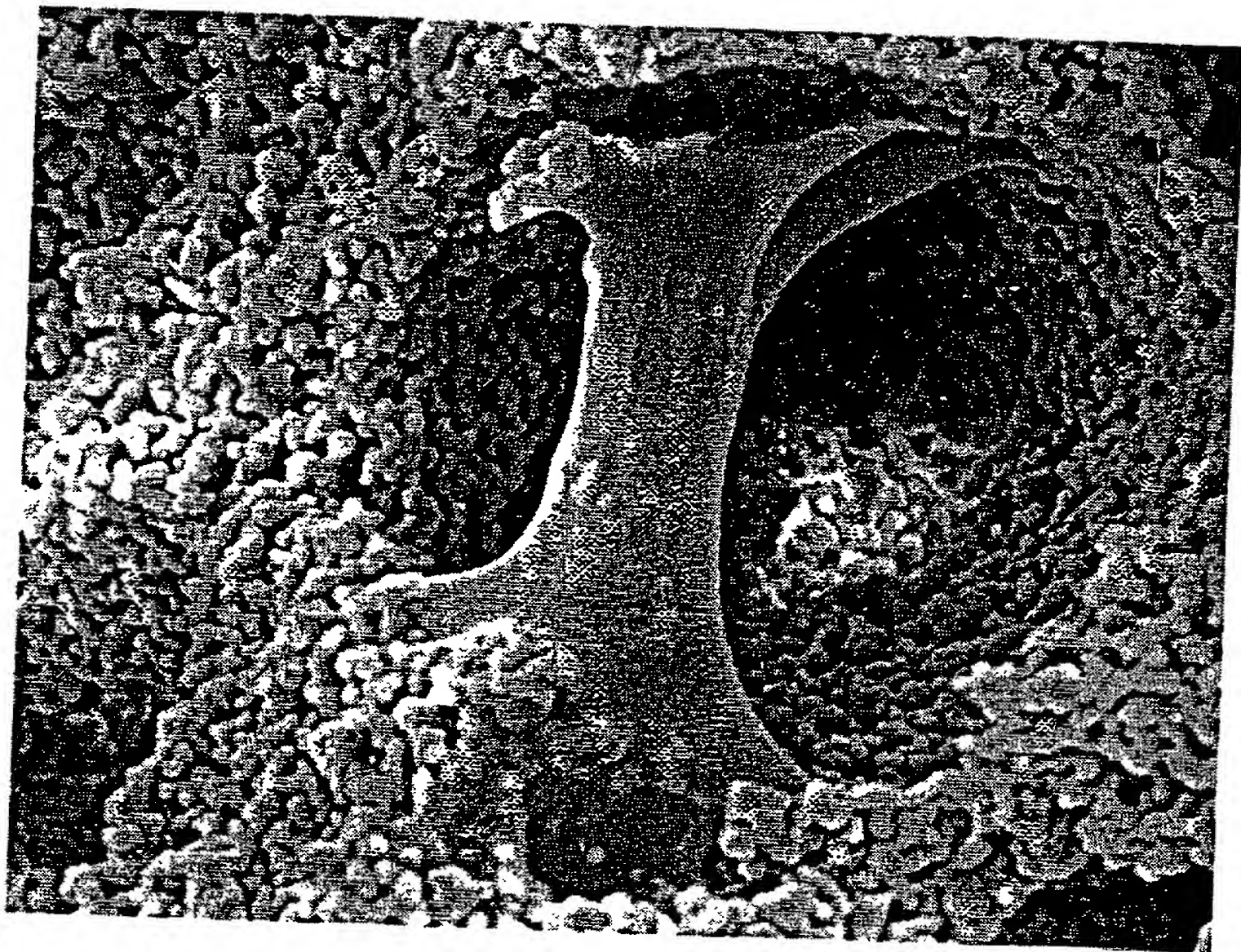


FIG. 5

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FIG. 6

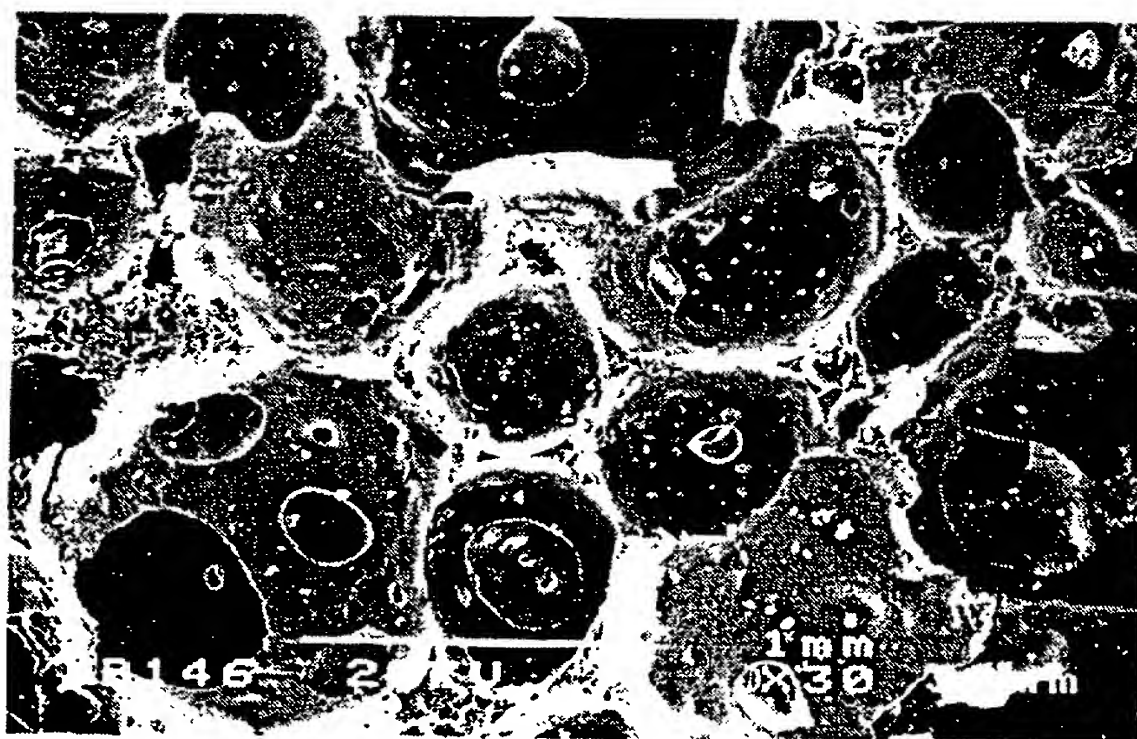


FIG. 7

SUBSTITUTE SHEET (RULE 26)

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DECLARATION FOR PATENT APPLICATION

Docket Number (optional) S1011/20102

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

PRODUCTION OF POROUS ARTICLES

The specification of which is attached hereto unless the following box is checked:

☒ Was filed on December 18, 1998 as United States Application Number or PCT International Application Number PCT/GB97/02705 and was amended on December 18, 1998 (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56. I hereby claim foreign priority benefits under 35 U.S.C. §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365 (a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Claimed

<u>9620752.7</u> (Number)	<u>GB</u> (Country)	<u>04.10.96</u> (Day/Month/Year Filed)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<u> </u> (Number)	<u> </u> (Country)	<u> </u> (Day/Month/Year Filed)	<input type="checkbox"/> Yes <input type="checkbox"/> No

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

<u> </u> (Application Number)	<u> </u> (Filing Date)
<u> </u> (Application Number)	<u> </u> (Filing Date)

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

<u>PCT/GB97/02705</u> (Application Number)	<u>OCTOBER 1, 1997</u> (Filing Date)	<u>(PENDING)</u> (Status-patented, pending, abandoned)
<u> </u> (Application Number)	<u> </u> (Filing Date)	<u> </u> (Status-patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

I, Alan H. Bernstein (Registration No. 19,315); Stanley H. Cohen (Registration No. 20,235); Manny D. Pokotilow (Registration No. 22,492); Barry A. Stein (Registration No. 25,257); Martin L. Faigus (Registration No. 24,364); Eric S. Marzluf (Registration No. 27,454); Robert S. Silver (Registration No. 35,681); Scott Slomowitz (Registration No. 39,032); Michael J. Berkowitz (Registration No. 39,607); David M. Tener (Registration No. 37,054) and James J. Kozuch (Registration No. 39,733)-care of Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd., 12th Floor, Seven Penn Center, 1635 Market Street, Philadelphia, Pennsylvania 19103-2212, my attorneys with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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